REMARKS

Entry and consideration of the Amendment is respectfully requested. Claim 11 has been amended to further clarify the invention. Claims 36-41 have been canceled. The subject matter of canceled claims 36-41 is found in new claims 108-113. After entry of the Amendment, claims 11, 31, 32, 34, 42, 43, and 108-113 are pending.

The amendment to claim 11 is supported throughout the specification, including at page 39, lines 15-21, and does not raise any issues of new matter. New claims 108-113 are supported throughout the specification, including at page 39, lines 1-20, page 40, lines 26-32 and do not raise any issues of new matter. Applicants submit the Amendment places the application in condition for allowance and does not raise any issues not previously considered by the Examiner.

Indefiniteness

The Examiner rejected claims 36-41 under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner asserts the term "specificity" in claims 36 and 39 is unclear that Applicants would be able to make an antibody with specificity of the antibody to SEQ ID NO: 16. Applicants disagree with this statement. As discussed previously, Applicants provided a definition for "specificity" at page 23, line 27. Applicants have also described several ways of characterizing and screening for antibodies having specificity at pages 40, line 26, to page 41, line 19. Applicants further submit the term specificity is understood by one of skill in the art. Without acquiescing to the rejection, but in order to address the Examiner's concern, Applicants have canceled claims 36-41 and present new claims 108-113 to clarify the subject matter of claims 36-41.

Applicants, therefore, respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph, rejection.

Utility

The Examiner rejected claims 11, 31, 32, 34, and 36-43 under 35 U.S.C. § 101 as lacking either a specific and /or substantial asserted utility or a well-established utility. Applicants respectfully traverse this rejection.

As discussed previously, Applicants have described a variety of uses of the claimed antibodies. Those uses include using the antibody to purify a polypeptide having a sequence of SEQ ID NO:16, (see page 41, lines 13-19), using the antibody as a diagnostic (see page 46, lines 19-29), to target delivery for a pharmaceutical agent to tissues (page 39, lines 1-5), and for use as an antagonist (see page 39, lines 1-5). Applicants assert any one of these described utilities are sufficient to establish utility of the claimed antibodies.

The Examiner asserts it is unclear how one skilled in the art would employ a diagnostic assay for islet tumor cell using SEQ ID NO:16 as a marker because SEQ ID NO:16 is different from the pancreatic polypeptide taught by Adrian et al. and it is unclear whether one skilled in the art would be able to distinguish between the secreted polypeptide from normal islet cells and tumor islet cells.

In order to violate 35 U.S.C. § 101, the claimed subject matter must be totally incapable of achieving a useful result. *Brooktree Corp v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992). A small degree of utility is sufficient to satisfy § 101. An invention does not lack utility merely because the particular embodiment disclosed in the specification lacks perfection or performs crudely, nor is it essential that the invention accomplish all of its intended functions. MPEP § 2107.01. If an invention is only partially successful in achieving a useful result, a rejection of the invention based on lack of utility is not appropriate. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

Applicants assert antibodies to SEQ ID NO:16, in the least, achieve a useful result in a diagnostic assay. Antibodies to SEQ ID NO:16 may be used to specifically identify islet cells in a tissue. This specific identification aspect of the claimed antibodies has "real world" utility in a diagnostic assay to identify hyperplasias of islet cells.

Demonstration of increased numbers of cells secreting pancreatic polypeptide has been described as a characteristic of type II hyperplasia of pancreatic islets (Data sheet

for Biogenex polyclonal antibody to pancreatic polypeptide, Ab No. 066P; copy enclosed). An increase in the number of islet cells secreting pancreatic polypeptide may be quantified using microscopic techniques or flow cytometry techniques employing an antibody to SEQ ID NO:16. The Examiner asserts one skilled in the art must be able to distinguish between polypeptide having an amino acid sequence of SEQ ID NO:16 from normal islet cell and tumor islet cells in a diagnostic assay. Applicants assert such a distinction is not necessary. In an embodiment, an antibody to SEQ ID NO:16 is used as the marker for islet cells (SEQ ID NO:16 is specifically expressed in islet cells and in islet cell tumor only, see specification at page 26, lines 33-34) and an antibody to pancreatic polypeptide is used as a marker for cells containing pancreatic polypeptide and the number of double positive cells is quantified using microscopic or flow cytometry techniques. Such a method may be used to monitor the therapeutic effectiveness of a course of treatment for the hyperplasia. A decrease in the number of double positive cells following treatment is associated with therapeutic effectiveness of the treatment regime.

Antibodies to SEQ ID NO:16 may also be used in immunohistopathological preparations of a sample of tissue from a biopsy allowing for accurate diagnosis by visually confirming abnormal patterns of islet cells associated with islet cell hyerplasias, including tumor. In this aspect of the invention, an antibody to SEQ ID NO:16 labeled with a fluorescent or enzymatic tag functions similar to a differential stain. Unlike traditional differential stains useful in histopathological preparations of tissue, however, the antibody is specific for a particular type of cell thereby minimizing non-specific background staining and allowing for specific visualization of a particular cell type in the tissue sample.

The Examiner asserts that even in situations were there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein. Applicants respectfully disagree.

Applicants do not have to provide evidence sufficient to establish that an asserted utility is true beyond a reasonable doubt. *In re Irons*, 340 F.2d 974, 978 (CCPA 1965). Nor do Applicants have to provide evidence that establishes the asserted utility as a

matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-867 (CCPA 1980). Rather, Applicants only have the burden of presenting evidence that leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. MPEP § 2107.02 (emphasis in original).

Brenner et al. teaches that pairwise sequence comparison methods are capable of detecting almost all relationships between proteins whose sequence identities are greater than 30% (Brenner et al., Abstract at page 6073 and figure 3 at page 6075). Brenner et al. also found that pairwise sequence comparison methods utilizing statistical scores, such as E-values, recognized greater than 90% of the homologous pairs with 30-40% identity (Brenner et al. at page 6077). Brenner et al. conclude that E-values give fairly accurate estimates of the significance of pairwise sequence matches and the homologous proteins found by sequence comparison can be distinguished with high reliability from the huge number of unrelated pairs. (Brenner et al. at pages 6077-6078).

Applicants' methods for identifying protein sequence homology were similar to the pairwise sequence comparison methods described in Brenner et al. See, for example, specification at pages 54-55. Brenner et al. teach that pairwise sequence comparison methods are capable of detecting almost all relationships between proteins whose sequence identities are greater than 30% (Brenner et al., Abstract at page 6073 and figure 3 at page 6075). Therefore, one skilled in the art would recognize that a functional assignment of EXCS based on the significant homology to pancreatic polypeptide, as shown in Table 2 in the specification, is more likely than not true.

Based on the forgoing, Applicants submit the claimed antibodies have specific and substantial utility as evidenced by the described real world uses and significant amino acid sequence homology to pancreatic polypeptide. Withdrawal of the rejection is respectfully requested.

Enablement

The Examiner rejected claims 11, 31, 32, 34, and 36-43 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner asserts one skilled in the art would not know how to use the claimed invention because the claimed invention is not

supported by either a specific and/or substantial asserted utility or a well-established utility. Applicants respectfully traverse this rejection.

Applicants have now directed the claims to an antibody that specifically binds a polypeptide comprising an amino acid sequence of SEQ ID NO: 16. Without acquiescing to the rejection and solely to expedite prosecution, Applicants have amended the claim to no longer refer to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 16 and a biologically active fragment having at least 90% identity with the amino acid of SEQ ID NO: 16. This amendment renders the basis of the Examiner's 112, first paragraph, rejection moot.

Applicants provide sufficient disclosure in the specification to enable the production of specific antibodies raised against specific antigens. See, for example, the specification at page 62, beginning at line 31 where Applicants describe how to produce EXCS specific antibodies. Based on this disclosure and the fact that the production of antibodies against a characterized antigen is a mature technology where the level of skill is high and advanced, Applicants assert one of skill in the art is enabled to make antibodies as claimed.

Based on the forgoing, Applicants assert the specification teaches one skilled in the art how to make and use the claimed invention. Withdrawal of the rejection is respectfully requested.

Written Description

The Examiner rejected claims 11, 31, 32, 34, and 36-43 under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicants respectfully traverse this rejection.

Applicants have now directed the claims to an antibody that specifically binds a polypeptide comprising an amino acid sequence of SEQ ID NO:16. Without acquiescing to the rejection and solely to expedite prosecution, Applicants have amended the claim to no longer refer to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 16 and a biologically active fragment having at least 90% identity with the amino acid of SEQ ID NO: 16.

Applicants have provided sequence data for the peptide antigen and structural information relating thereto. Exemplary is the disclosure of SEQ ID NO:16. In addition, homology information is disclosed which provides a reasonable basis to determine function. Therefore, Applicants assert that one of skill in the art would have recognized that the spectrum of antibodies that bind to SEQ ID NO:16 were disclosed as a result of the isolation of SEQ ID NO:16.

Based on the forgoing, Applicants assert the specification reasonably conveys to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Withdrawal of the rejection is respectfully requested.

Novelty

The Examiner rejected claims 11, 37, 40, and 42-43 under 35 U.S.C. § 102(b) as anticipated by Adrian et al., 1986, *New Engl. J. Med.*, 315:287-291 as evidenced by Bost et al., 1988, *Immunol. Invest.*, 17:577-586 and Benadayan, M., 1995, *J. Histochem. Cytochem.*, 43:881-886 and the known fact disclosed in the specification in Table 2, 2nd row. Applicants respectfully traverse this rejection.

Adrian et al. disclose rabbit antibody to a human pancreatic polypeptide. The Examiner asserts binding to SEQ ID NO:16 is an inherent property of the reference antibodies as evidenced by Table 2 of the specification and two pieces of extrinsic evidence, Bost et al. and Bendayan et al. Applicants respectfully disagree.

To anticipate a claim, each and every element of the claim must be described, either expressly or inherently, in a single prior art reference. Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631 (Fed. Cir. 1987). The Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The prior inherent characteristic must be established as a certainty, probabilities are not sufficient. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). Adrian et al. does not teach or suggest that the

antibody described therein would necessarily or for certain bind specifically to a polypeptide comprising an amino acid sequence of SEQ ID NO:16..

The human pancreatic polypeptide as disclosed by Adrian et al. does not have an amino acid sequence of SEQ ID NO: 16. SEQ ID NO: 16 has an amino acid sequence of 178 amino acids wherein the pancreatic polypeptide of Adrian et al. has 36 amino acids. Leiter et al., 1985, *J. Biol. Chem.*, 260:13013-13017, discloses the amino acid sequence of a 36 amino acid human pancreatic polypeptide and a 95 amino acid precursor polypeptide. Both of these sequecne differ in size and amino acid composition from a polypeptide comprising SEQ ID NO: 16. The difference in size and amino acid sequence shows that there is no certainty that the antibody as described in Adrian would bind to a polypeptide comprising an amino acid sequence of SEQ ID NO: 16. Nothing in the Adrian reference necessarily suggests the disclosed antibodies specifically bind polypeptides having an amino acid sequence of SEQ ID NO: 16.

The Examiner maintains the inherent property of the reference antibodies are evidenced by two pieces of extrinsic evidence, Bost et al. and Bendayan et al. Multiple reference rejections under 35 U.S.C. § 102 are proper when the references are cited to show that a characteristic not disclosed in the primary reference is inherent. MPEP § 2131.01. "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the [primary] reference, and that it would be so recognized by persons of ordinary skill." Continental Can v. Monsanto, 948 F.2d 1264, 1268 (Fed. Cir. 1991). MPEP § 2131.01, part III.

Neither Bost et al. nor Bendayan et al. make clear that specifically binding SEQ ID NO: 16 is necessarily a property of the antibodies disclosed by Adrian et al. The references disclose the possibility that an antibody to some antigens may specifically bind two different proteins and describe epitopes that may give rise to cross-reactivity. The references are directed to antibodies to different polypeptides than that of a polypeptide comprising SEQ ID NO:16. These references do not necessarily show or certainly show that the crossreactivity is a property of the antibodies of Adrian et al.. The prior inherent

characteristic must be established as a certainty, probabilities are not sufficient. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). Therefore, neither Bost et al. nor Bendayan et al. teach that the antibodies disclosed by Adrian et al. necessarily bind SEQ ID NO:16.

Based on the foregoing, Applicants respectfuly request withdrawal of the rejection.

Obviousness

The Examiner rejected claim 31 under 35 U.S.C. § 103(a) as obvious over Adrian et al., 1986, *New Engl. J. Med.*, 315:287-291 as evidence by Bost et al., 1988, *Immunol. Invest.*, 17:577-586 and Benadayan, M., 1995, *J. Histochem. Cytochem.*, 43:881-886 and the known fact disclosed in the specification in Table 2, 2nd row in view of Owens et al. Applicants respectfully traverse this rejection.

Applicants submit the Office Action fails to establish a *prima facie* case of obviousness. The Examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. MPEP § 2142. Three criteria must be met by the Examiner to establish a prima facie case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). The Examiner has failed, in the least, to establish that the cited references teach or suggest all of the claim limitations.

As discussed above, Adrian et al. does not teach or suggest an antibody that specifically binds to SEQ ID NO:16. The human pancreatic polypeptide disclosed by Adrian et al. does not have an amino acid sequence or the size of a polypeptide comprising SEQ ID NO:16. Neither Bost et al. nor Bendayan et al. make clear that binding of a polypeptide comprising SEQ ID NO:16 is necessarily a property of the antibodies disclosed by Adrian et al. The Bost and Bendayan references disclose the possibility that an antibody may specifically bind two different proteins and describe epitopes that may give rise to cross-reactivity among two different proteins. These

references describe antibodies to different polypeptides than a polypeptide comprising SEQ ID NO:16 . The structure and sequence of the polypeptides disclosed in Bendayan etal, Bost et al and Adrian et al are different than that of a polypeptide comprising SEQ ID NO:16, and therefore, do not teach or suggest that the antibodies to a polypeptide that have a different sequence, length, and/or three dimensional structure would be crossreactive. Therefore, neither Bost et al. nor Bendayan et al. alone or in combination with Adrian et al. teach or suggest that the antibodies disclosed by Adrian et al. necessarily bind SEQ ID NO:16.

Owens et al. does not remedy the shortcomings of Adrian et al. and the secondary references of Bost and Bendayan. Owens et al. describes modification of murine antibodies. Owens et al., however, does not teach or suggest an antibody that binds SEQ ID NO:16.

Based on the forgoing, Applicants submit the Examiner has failed to establish a *prima facie* case of obviousness. The Examiner has failed, in the least, to establish that the cited references teach or suggest all of the claim limitations. Withdrawal of the rejection is respectfully requested.

The Examiner rejected claim 23 under 35 U.S.C. § 103(a) as obvious over Adrian et al., 1986, *New Engl. J. Med.*, 315:287-291 as evidence by Bost et al., 1988, *Immunol. Invest.*, 17:577-586 and Benadayan, M., 1995, *J. Histochem. Cytochem.*, 43:881-886 and the known fact disclosed in the specification in Table 2, 2nd row in view of Bird et al., Applicants respectfully traverse this rejection.

Applicants submit the Office Action fails to establish a *prima facie* case of obviousness. The Examiner has failed, in the least, to establish that the cited references teach or suggest all of the claim limitations.

As discussed above, Adrian et al. does not teach or suggest an antibody that specifically binds to SEQ ID NO:16. The Bost and Bendayan references do not teach or suggest that the described epitopes are present in human pancreatic polypeptide and/or SEQ ID NO:16 nor do the references teach or suggest that the antibodies disclosed by Adrian et al. specifically bind the described epitopes. These references describe antibodies to different polypeptides than a polypeptide comprising SEQ ID NO:16 . The

structure and sequence of the polypeptides disclosed in Bendayan etal, Bost et al and Adrian et al are different than that of a polypeptide comprising SEQ ID NO:16, and therefore, do not teach or suggest that the antibodies to a polypeptide that have a different sequence, length, and/or three dimensional structure would be crossreactive. Therefore, neither Bost et al. nor Bendayan et al. alone or in combination with Adrian et al. teach or suggest that the antibodies disclosed by Adrian et al. necessarily bind SEQ ID NO:16.

Bird et al. does not remedy the shortcomings of Adrian et al. and the secondary references of Bost and Bendayan. Bird et al. teaches single chain antibodies. Bird et al., however, does not teach or suggest an antibody that binds SEQ ID NO:16.

Based on the forgoing, Applicants submit the Examiner has failed to establish a *prima facie* case of obviousness. The Examiner has failed, in the least, to establish that the cited references teach or suggest all of the claim limitations. Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 36 and 39 under 35 U.S.C. § 103(a) as obvious over Adrian et al., 1986, *New Engl. J. Med.*, 315:287-291 as evidence by Bost et al., 1988, *Immunol. Invest.*, 17:577-586 and Benadayan, M., 1995, *J. Histochem. Cytochem.*, 43:881-886 and the known fact disclosed in the specification in Table 2, 2nd row in view of Harlow et al., Applicants respectfully traverse this rejection.

Applicants submit the Office Action fails to establish a *prima facie* case of obviousness. The Examiner has failed, in the least, to establish that the cited references teach or suggest all of the claim limitations.

As discussed above, Adrian et al. clearly does not teach or suggest an antibody that specifically binds to SEQ ID NO:16. Neither Bost et al. nor Bendayan et al. make clear that binding SEQ ID NO:16 is not necessarily a property of the antibodies disclosed by Adrian et al. The Bost and Bendayan references do not teach or suggest that the described epitopes are present in human pancreatic polypeptide and/or SEQ ID NO:16 nor do the references teach or suggest that the antibodies disclosed by Adrian et al. specifically bind the described epitopes. These references describe antibodies to different polypeptides than a polypeptide comprising SEQ ID NO:16. The structure and sequence

of the polypeptides disclosed in Bendayan etal, Bost et al and Adrian et al are different than that of a polypeptide comprising SEQ ID NO:16, and therefore, do not teach or suggest that the antibodies to a polypeptide that have a different sequence, length, and/or three dimensional structure would be crossreactive. Therefore, neither Bost et al. nor Bendayan et al. alone or in combination with Adrian et al. teach or suggest that the antibodies disclosed by Adrian et al. necessarily bind SEQ ID NO:16.

Harlow et al. does not remedy the shortcomings of Adrian et al. and the secondary references of Bost and Bendayan. Harlow et al. teaches a method of producing polyclonal antibody to any antigen. Harlow et al., however, does not teach or suggest an antibody that binds SEQ ID NO:16. This is a general methodology text.

Based on the forgoing, Applicants submit the Examiner has failed to establish a *prima facie* case of obviousness. The Examiner has failed, in the least, to establish that the cited references teach or suggest all of the claim limitations. Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 32, 34, 38, and 41 under 35 U.S.C. § 103(a) as obvious over Adrian et al., 1986, *New Engl. J. Med.*, 315:287-291 as evidence by Bost et al., 1988, *Immunol. Invest.*, 17:577-586 and Benadayan, M., 1995, *J. Histochem. Cytochem.*, 43:881-886 and the known fact disclosed in the specification in Table 2, 2nd row in view of U.S. Patent No. 5,766,910 (hereinafter the '910 patent). Applicants respectfully traverse this rejection.

Applicants submit the Office Action fails to establish a *prima facie* case of obviousness. The Examiner has failed, in the least, to establish that the cited references teach or suggest all of the claim limitations.

As discussed above, Adrian et al. clearly does not teach or suggest an antibody that specifically binds to SEQ ID NO:16. Neither Bost et al. nor Bendayan et al. make clear that binding SEQ ID NO:16 is necessarily a property of the antibodies disclosed by Adrian et al. These references describe antibodies to different polypeptides than a polypeptide comprising SEQ ID NO:16 . The structure and sequence of the polypeptides disclosed in Bendayan etal, Bost et al and Adrian et al are different than that of a polypeptide comprising SEQ ID NO:16, and therefore, do not teach or suggest that the

antibodies to a polypeptide that have a different sequence, length, and/or three dimensional structure would be crossreactive. Therefore, neither Bost et al. nor Bendayan et al. alone or in combination with Adrian et al. teach or suggest that the antibodies disclosed by Adrian et al. necessarily bind SEQ ID NO:16.

The '910 patent does not remedy the shortcomings of Adrian et al. and the secondary references of Bost and Bendayan. The '901 patent teaches a pharmaceutical acceptable carriers useful in pharmaceutical compositions comprising antibodies. The '901 patent, however, does not teach or suggest an antibody that binds SEQ ID NO:16.

Based on the forgoing, Applicants submit the Examiner has failed to establish a *prima facie* case of obviousness. The Examiner has failed, in the least, to establish that the cited references teach or suggest all of the claim limitations. Withdrawal of the rejection is respectfully requested.

Conclusion

In light of the foregoing amendment and remarks, Applicants' assert the claims are in condition for allowance. Removal of all rejections and early notice of allowable claims is requested.

The Examiner is invited to telephone the undersigned attorney for clarification of any of these remarks or amendments, or to otherwise speed prosecution of this case.

Respectfully submitted,

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